Research Article

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Efficacy And Safety of Coadministration of Tolvaptan And Carperitide for Acute Decompensated Heart Failure Patients

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Abstract

For acute decompensated heart failure (ADHF) therapy, combination of carperitide, a human atrial natriuretic peptide, and tolvaptan, a novel vasopressin type 2 receptor antagonists, has not been used. Tolvaptan is a drug newly developed to treat volume overload in ADHF patients. Of 102 consecutive cases treated upon admission for ADHF between April and October 2012, we analyzed 51 patients treated with carperitide plus tolvaptan (tolvaptan +carperitide group) and 51 patients treated with carperitide plus conventional diuretics (carperitide group). On comparison between both groups, total dose of carperitide and loop diuretic doses during 48 h in tolvaptan +carperitide group were lower than those in the carperitide group (both $p<0.001$). Urine output at 24 h and 48 h after admission in the tolvaptan+carperitide group were significantly higher than those in carperitide group ($p=0.02$ and $p<0.001$, respectively). Changes in NT-pro brain-type natriuretic peptide levels in tolvaptan+carperitide group were significantly higher than those in carperitide group ($p=0.01$). No significant differences were detected in worsening renal function. On conclusion, in ADHF therapy, coadministration of tolvaptan and carperitide was more effective and safe compared with conventional therapy.

Introduction

Diuretics are used to reduce venous congestion and control body fluid retention in acute decompensated heart failure (ADHF). Loop diuretics have a particularly potent diuretic effect and are still often used. The acute decompensated heart failure syndromes (ATTEND) registry in Japan states that loop diuretics were administered to approximately 90% of hospitalized patients in Japan [1]. However, loop diuretics have been reported to cause electrolyte abnormality, affect kidney function, activate neurohumoral factors and show a correlation with mortality rate. Loop diuretic administration is problematic in ADHF and attention is now being focused on renal protection.

Carperitide, an α-human atrial natriuretic peptide synthesized using genetic recombination [2] has been used to treat ADHF in Japan. It has vasodilator and diuretic actions as well as an inhibitory effect on the renin–angiotensin–aldosterone system (RAAS). According to the ATTEND registry, carperitide was administered to approximately 60% of hospitalized patients in Japan [3]. Its therapeutic effects in the acute phase and an improvement in long-term prognoses have been reported [3,4] However, administration has been difficult in patients with low blood pressure and/or low cardiac output [5]. Tolvaptan, a novel diuretic, inhibits vasopressin V2 receptors in the renal collecting ducts. Its mechanism of action differs from that of existing diuretics: it is an aquaretic, i.e., it does not cause changes in kidney circulation or electrolytes and does not affect hemodynamics [6]. In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan study, tolvaptan was reported to increase urinary volume,

reduce body weight, and alleviate edema [7]. Compared with existing diuretics, tolvaptan achieved significant urinary volume in patients 48 h after the initial administration. It shows a reduced worsening renal function (WRF) incidence [8]. There have been no reports of their concurrent administration of carperitide and tolvaptan thus far. Therefore, we evaluated the effect, safety, and prognosis of coadministration of tolvaptan and carperitide in ADHF patients.

Methods

Study population

This study was a prospective study involving 102 patients diagnosed with ADHF between April and October 2012, who also showed body fluid retention and had received carperitide. The attending physician diagnosed ADHF based on the Framingham criteria [9]. Body fluid retention was diagnosed based on pleural effusion, edema, and overhydration. Patients with acute myocardial infarction, cardiogenic shock, tracheal intubation, hypernatremia, or hyperkalemia were excluded from the study. The study protocol was prepared in accordance with the Helsinki Declaration. All patients provided their approval by signing an informed consent form. This study was approved by the local ethics committee.

The patients were divided into two groups: tolvaptan+carperitide group received carperitide and tolvaptan in combination and carperitide group received carperitide alone or in combination with existing diuretics. The treatment method was selected at the discretion of the attending physician.

Procedures

The initial treatment was administered to patients diagnosed with cardiac failure and found to have body fluid retention such as pleural effusion and edema. These patients were started on carperitide 0.0125-0.025 µg/kg/min after admission. The patients in the tolvaptan +carperitide group were started on oral tolvaptan 3.75 mg/day-15 mg/day simultaneously. Tolvaptan was discontinued when daily urinary output ≥ 5000 ml/day, Na>145 mEq/L, or K>4.5 mEq/L was achieved or when improvements in body fluid retention were observed. The carperitide group was started on 0.0125-0.025 µg/kg/min, and the dose was increased in line with changes in blood pressure and urinary output. If urinary output remained insufficient, loop diuretic furosemide was added.
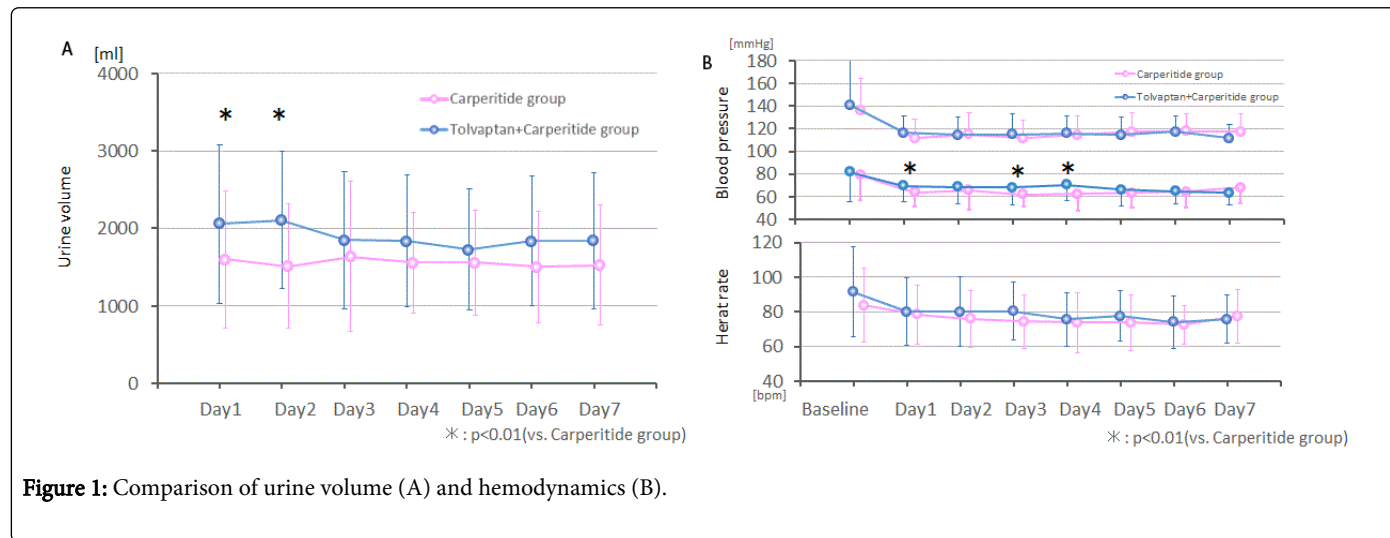

Figure 1: Comparison of urine volume (A) and hemodynamics (B).

	Tolvaputan+carperitide group (n=51)	Carperitide group (n=51)	p value
Age (years)	76.2 ± 12.0	77.4 ± 12.6	n.s.
Gender (male)	27 (52.9%)	30(58.8%)	n.s.
BMI	21.0 ± 4.3	21.8 ± 4.0	n.s.
Smokers	18 (35.3%)	17 (33.3%)	n.s.
Hypertension	36 (70.6%)	44 (86.3%)	n.s.
Diabetes mellitus	15 (29.4%)	18 (35.3%)	n.s.
Dyslipidemia	15 (29.4%)	17 (33.3%)	n.s.
Cerebral infarction	3 (5.9%)	4 (7.8%)	n.s.
Atrial fibrillation	21 (41.2%)	17 (33.3%)	n.s.
Ischemic heart disease	23 (46.0%)	22 (43.1%)	n.s.
History of heart failure	33 (64.7%)	26 (51.0%)	n.s.
Etiology			
Arrhythmia	9 (17.7%)	15 (29.4%)	**n.s**
Ischemic heart disease	15 (29.4%)	21 (38.9%)	
Valvular disease	6 (11.8%)	3 (5.9%)	
Dilated cardiomyopathy	12 (23.5%)	7 (13.7%)	
Other	9 (17.7%)	5 (9.8%)	
Concomitant medication			

ACE inhibitors or ARBs	45 (88.2%)	36 (70.6%)	n.s.
β-blockers	37 (72.6%)	33 (64.1%)	n.s.
Ca-blockers	11 (21.6%)	12 (23.5%)	n.s.
Loop diuretics	43 (84.3%)	39 (76.5%)	n.s.
Spironolactone	29 (56.9%)	11 (21.6%)	<0.01
NYHA II	2 (3.9%)	2 (3.9%)	n.s.
III	20 (39.2%)	19 (37.3%)	n.s.
IV	29 (56.9%)	30 (58.8%)	n.s.
Clinical scenario 1	20 (39.2%)	20 (39.2%)	n.s.
2	20 (39.2%)	27 (52.9%)	
3	8 (15.7%)	4 (7.8%)	
5	3 (5.9%)	0	
Systolic blood pressure (mmHg)	141.0 ± 39.0	136.2 ± 27.8	n.s.
Diastolic blood pressure (mmHg)	81.7 ± 26.2	78.8 ± 21.4	n.s.
Heart rate (/min)	91.4 ± 25.8	83.8 ± 21.1	n.s.
Serum creatinine (mg/dl)	1.5 ± 0.8	1.3 ± 0.6	n.s.
Estimated GFR (mL/min/1.73m^2)	38.8 ± 20.2	43.2 ± 21.7	n.s.
Serum sodium (mEq/L)	138.6 ± 5.2	138.2 ± 3.8	n.s.
Serum potassium (mEq/L)	4.2 ± 0.6	4.1 ± 0.5	n.s.
NT-pro BNP (pg/ml)	17486.8 ± 25689.4	7774.0 ± 8291.5	0.01
Echocardiography			
left atrium volume index (ml/m^2)	47.7 ± 22.5	36.4 ± 14.9	<0.01
Left ventricular end diastolic diameter (mm)	52.8 ± 9.3	50.6 ± 9.8	n.s.
Left ventricular end systolic diameter (mm)	42.4 ± 11.5	39.4 ± 10.7	n.s.
Left ventricular end diastolic volume (ml)	128.8 ± 74.9	105.7 ± 49.5	n.s.
Left ventricular end systolic volume (ml)	83.4 ± 67.3	63.7 ± 42.8	n.s.
Left ventricular ejection fraction (%)	40.3 ± 16.7	44.5 ± 14.5	n.s.
Medication			
Dose of tolvaptan (mg/day)	12.7 ± 3.5		
Duration of administration [day] (IQR)	3 (3-8)		
Dose of carperitide (μg/kg/min)	0.024 ± 0.013	0.037 ± 0.023	<0.01
Total dose of carperitide (μg)	1660 ± 1310	2470 ± 2300	0.03
Duration of administration [day] (IQR)	8.0 (5-14)	7.0 (5-10)	n.s.
Dose of intravenous furosemide for 48 h (mg)	11.4 ± 16.6	29.2 ± 30.6	<0.001
Nitroglycerin	13 (25.5%)	9 (17.7%)	n.s.
Cardiac stimulant	15 (29.4%)	8 (15.7%)	n.s.

Non-invasive positive-pressure ventilation	16 (31.4%)	17 (33.3%)	n.s.
Duration of hospitalization (day)	23.3 ± 25.1	24.7 ± 24.2	n.s.

Table1: Patient background and demographic data. BMI: Body Mass Index; ACE: Angiotensin-Converting Enzyme; ARB: Angiotensinreceptor Blocker; NYHA: New York Heart Association; EGRF: Estimated Glomerular Filtration Rate; BNP: Brain-Type Natriuretic Peptide; IQR: Interquartile Range.

Data collection

All data were prospectively collected. The study subjects were surveyed regarding etiology of heart failure, New York Heart Association functional class, hypertension, dyslipidemia, and diabetes mellitus. Patients were deemed to have hypertension if they had a history of hypertension or if they were being treated for the condition. Dyslipidemia was defined in patients with serum total cholesterol level>220 mg/dL or those being treated for the condition. Current or past smokers were defined as smokers. Diabetes mellitus was defined based on the World Health Organization (WHO) criteria or in patients being treated for the condition. Electrocardiography, chest X-ray, and echocardiography were performed before tolvaptan or carperitide administration. Using echocardiography, we measured the left ventricular end systolic and diastolic diameter, left ventricular end systolic and diastolic volume, left ventricular ejection fraction, and left atrial volume index. Data including heart rate; blood pressure; body weight; daily urine volume; and serum creatinine, sodium, potassium, and NT-pro brain-type natriuretic peptide (NT-proBNP) levels were measured at baseline and on days 1, 2, 3, 5, and 7 after the start of treatment. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease study equation coefficients modified for Japanese patients [10]. Body fluid retention was defined as lower limb edema, pleural effusion retention, and/or ascites and was observed using physical findings and chest X-ray imaging. We assessed patients until body fluid retention resolved. WRF was defined as serum creatinine elevation of 0.3 mg/dL or 50% above baseline within 48 h [11]. Regarding safety, change between serum Na level at admission and maximum levels during treatment was determined to study possible correlation with hypernatremia, a known adverse reaction associated with tolvaptan. We also evaluated urinary output in patients with reduced left ventricular contractility (ejection fraction<30%), patients with moderate to severe kidney dysfunction (eGFR<30 ml/min/1.73 m^2), and patients with hypotension at admission (systolic blood pressure<110 mmHg). Adverse events, defined as death due to exacerbation of cardiac failure during hospitalization (severe adverse event), hypotension, hypernatremia, and liver disorder, were evaluated in all patients. Hypotension was defined as systolic blood pressure of <90 mmHg or onset of symptoms induced by hypotension. Long-term prognosis was defined as cardiovascular death or rehospitalisation due to ADHF, and in this situation, patients were then observed for 730 days on outpatient basis.

Statistical analysis

All the continuous data were represented as mean ± standard deviation or median [range or 25%-75% interquartile range (IQR)]. Unpaired Student's t-test was used for two-group comparisons relating to the continuous variable. Paired t-test was used to examine changes from the baseline in blood pressure, heart rate, daily urine volume, blood samples data, and echocardiographic data. If the data were not distributed normally, the Mann-Whitney U test was used. Chi-square test was used for proportional comparison. A t-test was used to calibrate the correlation between two indices. Kaplan-Meier curves were used for long-term mortality rates and readmissions and the two groups were compared using the log-rank test. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed with a standard statistical program package (JMP 10, SAS Institute, Cary, NC).
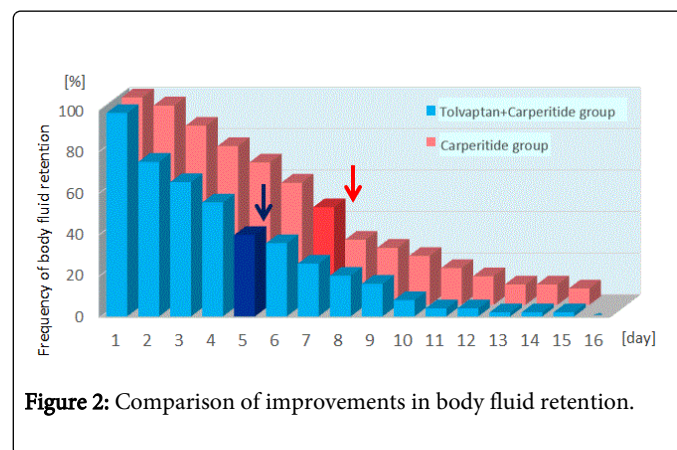

Figure 2: Comparison of improvements in body fluid retention.

Results

Patient background

During the study period, 102 patients with ADHF were enrolled. The baseline patient characteristics are shown in Table 1. Of these patients, 51 were in the tolvaptan+carperitide group, and 51 were in the carperitide group. There were no intergroup differences in terms of age, sex, or underlying disease. A history of hospitalization with cardiac failure was found in 33 (64.7%) of the patients in the tolvaptan+carperitide group and in 26 patients (51.0%) in the carperitide group. No intergroup differences in terms of administration of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β blockers, statins, Ca-blockers, or loop diuretics were observed. More patients in the tolvaptan+carperitide group (n=29, 56.9%) were taking oral aldosterone antagonists than in the carperitide group (n=11, 21.6%). The majority of the patients were classified as wet and warm (tolvaptan+carperitide group 84.3%, carperitide group 88.2%) based on the Nohria/Stevenson classification. Based on the Clinical scenario (CS) classification, 39.2% of patients in both groups were classified as CS1 associated with body fluid retention, 39.2% of patients in tolvaptan+carperitide group and 52.9% of patients in carperitide group were classified as CS2, whereas 15.7% of the tolvaptan+carperitide group and 7.8% of the carperitide group were classified as CS3. No intergroup differences based on the results of cardiac ultrasounds were observed.

Administered drugs and therapy

The results of medication administered during inpatient treatment are shown in Table 1. Mean dose of tolvaptan in the tolvaptan+carperitide group was 12.7 ± 3.5 mg/day, and the median dosing period was 3 (IQR 3-8) days. Mean administered dose of carperitide was significantly lower in the tolvaptan+carperitide group than in the carperitide group (tolvaptan+carperitide group 0.024 ± 0.013 μg/kg/min, carperitide group 0.037 ± 0.023 μg/kg/min, p<0.01). Similarly, mean dose of loop diuretics administered within 48 h of admission was significantly higher in the carperitide group than in the tolvaptan+carperitide group (tolvaptan+carperitide group 11.4 ± 16.6 mg, carperitide group 29.2 ± 30.6 mg, p<0.001). No differences in the dosing ratios of nitroglycerin and cardiac stimulants were observed. No intergroup difference was observed in duration of hospitalization (tolvaptan+carperitide group 23.3 ± 25.1/day, carperitide group 24.7 ± 24.2/day).
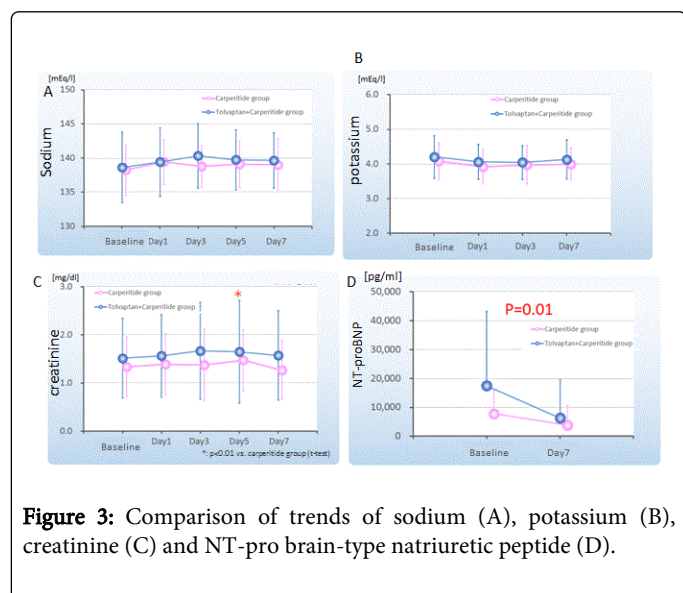

Figure 3: Comparison of trends of sodium (A), potassium (B), creatinine (C) and NT-pro brain-type natriuretic peptide (D).

	Tolvaputan+carperitide group (n=51)	Carperitide group (n=51)	p value
In-hospital mortality	0	0	n.s.
Hypernatremia	1 (2.0%)	0	n.s.
Hypotension	1 (2.0%)	6 (11.8%)	<0.05
Hepatopathy	0	0	n.s.

Table 2: Comparison of adverse events.

Comparison of improvements in urine volume, body fluid retention, hemodynamics and laboratory data

Changes in mean urine volume are shown in Figure 1A. The urine volume was significantly higher in the tolvaptan+carperitide group than in the carperitide group on days 1 and 2 (day 1: tolvaptan+carperitide group 2059 ± 1025 ml *vs.* carperitide group 1601 ± 883 ml, p=0.02; day 2: 2107 ± 889 ml *vs.* 1512 ± 805 ml, p<0.01). The duration of treatment and proportion of patients with improved body fluid retention are shown in Figure 2. More patients in the tolvaptan+carperitide group tended to have improvements in body fluid

retention at an earlier stage, and the median timeframe of this improvement was 5 (IQR 2-8) days in the tolvaptan+carperitide group and 7 days (IQR 5-10) days in the carperitide group, which is significantly different (p<0.01). NT-proBNP levels decreased from the time of admission to discharge in both groups, but the reduction was statistically significant only in the tolvaptan+carperitide group (Figure 3). However, NT-proBNP at admission was significantly higher in the tolvaptan+carperitide group (17486.8 ± 25689.4 pg/ml *vs.* 7774.0 ± 8291.5 pg/ml, p=0.01). There were no significant intergroup differences in creatinine changes. No significant changes in Na or K levels were noted between the two groups (Figure 3).

There were no changes in either group in systolic blood pressure or heart rate. Diastolic blood pressure was significantly higher in the tolvaptan+carperitide group on days 1, 3, and 4 than in the carperitide group (Figure 1B).

WRF comparison

WRF occurred in 17.6% patients in the tolvaptan+carperitide group and in 15.7% patients in the carperitide group, showing no significant difference. The incidence of WRF in the 26 patients with ejection fraction<30% was 1/17 case (5.9%) in the tolvaptan+carperitide group, which was significantly lower compared with 2/9 cases (22.2%) in the carperitide group.

Safety comparison

Figure 4 shows the correlation between the pre-treatment serum Na levels and maximum changes in the tolvaptan+carperitide group. These parameters showed a negative correlation (r=0.55, p<0.001). Only one case of hypernatremia occurred in a patient whose serum Na levels reached 146 mEq/L. Patients with a serum Na level of ≤ 135 mEq/L at admission had a maximum increase in their serum Na level of 5.0 ± 5.4 mEq/L, compared with 0.2 ± 3.6 mEq/L in patients with serum Na levels>135 mEq/L; thus, a significant improvement was observed in the hyponatremia group (p<0.01).

Comparison of urine volume in patients with left ventricular systolic dysfunction, hypotension and chronic kidney disease

Figure 5A shows the comparison of total urine output in 48 h in patients with ejection fraction<30%, systolic blood pressure of <110 mmHg at the start of treatment, and eGFR<30 ml/min/1.73 m². Under all these conditions, urine output was significantly higher in the tolvaptan+carperitide group. Figure 5B shows the relationship between left ventricle ejection fraction and total urine output up to 48 h after the start of treatment. Although no correlation between ejection fraction and urine volume was observed in the carperitide group (r=0.05, p=0.72), there was a negative correlation in the tolvaptan+carperitide group (r=0.38, p<0.01). In patients whose EF was ≥ 45%, no differences between the tolvaptan+carperitide and carperitide groups (3432.1 ± 1826.5 ml vs. 3354.32 ± 1301.4 ml). In contrast, patients with ejection fraction<45% in the tolvaptan+carperitide group had significantly higher urine output compared with their counterpart subjects in the Carperitide group (4557.2 ± 1413.3 ml vs. 2825.4 ± 1458.3 ml, p<0.001). Therefore, even in patients with poor left ventricle contractility, the tolvaptan+carperitide group had a greater urine output in the first 48 h of treatment than in the carperitide group.
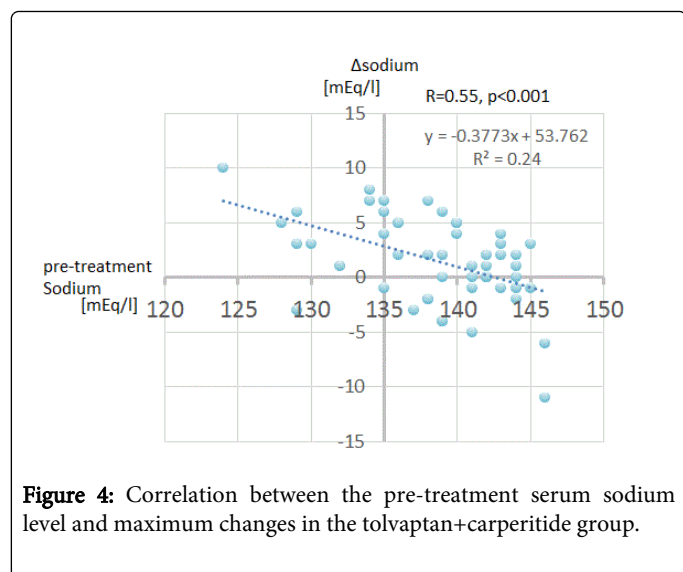
Figure 4: Correlation between the pre-treatment serum sodium level and maximum changes in the tolvaptan+carperitide group.

Drug cost comparison

Mean total drug cost per patient tended to be lower in the tolvaptan +carperitide group (48,397 ± 33,480 yen) than in the carperitide group (59,127 ± 52,109 yen), with a difference in mean cost of 10,730 yen.

Adverse events and long-term outcomes

The adverse events are shown in Table 2. There was one patient with hypernatremia in the tolvaptan+carperitide group; however, clinically, this patient was not problematic. Hypotension was significant and more frequent in the carperitide group (one case, 2.0% *vs.* 6 cases, 11.8%). No in-hospital deaths or liver disorders occurred. The results of long-term observation (730 days) showed no significant differences between the groups in terms of re-exacerbation of cardiac failure or cardiac death, but the prognosis tended to be better in the tolvaptan+carperitide group (Figure 6).
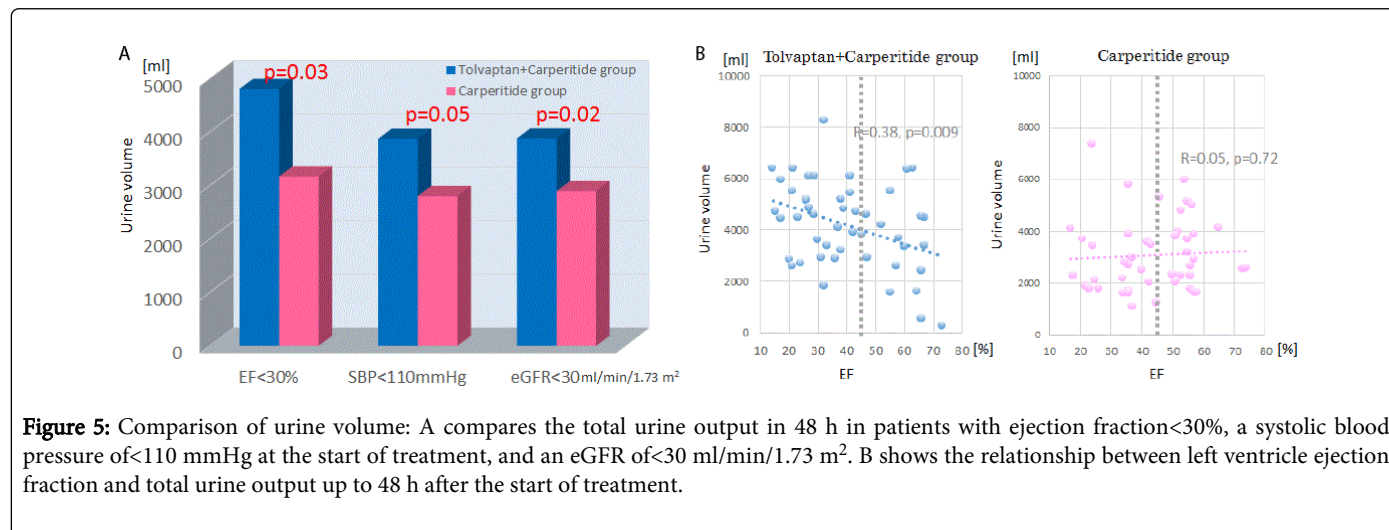

Figure 5: Comparison of urine volume: A compares the total urine output in 48 h in patients with ejection fraction<30%, a systolic blood pressure of<110 mmHg at the start of treatment, and an eGFR of<30 ml/min/1.73 m². B shows the relationship between left ventricle ejection fraction and total urine output up to 48 h after the start of treatment.

Discussion

For the first time, we demonstrated the efficacy and safety of a combination treatment using tolvaptan and carperitide for ADHF in comparison with the standard carperitide treatment. There were two major findings from this study: (1) Tolvaptan and carperitide used concurrently during the early stages of ADHF allowed for a greater reduction in the dose of loop diuretics than the standard treatment with carperitide and diuretics. A significant urine output in the acute stage without adverse effects on the hemodynamics was observed. There was no electrolyte imbalance or WRF increase. A shorter period of body fluid retention was also observed. (2) The combination produced similar effects even in patients with hypotension or reduced left ventricle function.

In this study, urine output was significantly higher on days 1 and 2 in the tolvaptan+carperitide group than in the carperitide group. According to a report comparing two groups of patients treated for ADHF with existing diuretics alone or in combination with tolvaptan, the group with the concurrent use of tolvaptan had significantly higher urine output in the first 48 h [8]. The results of the Acute Heart Failure Volume Control Multicenter (AVCMA) trial, which compared the effects of carperitide and tolvaptan, showed a high urine output during the 3 days after starting administration of tolvaptan, whereas no peak in the urine output change was observed in the Carperitide treatment group [12]. Therefore, the significantly higher urine output observed in our study during the first 2 days of treatment in the tolvaptan +carperitide group could be attributed to the additional tolvaptan. The mechanism of action of tolvaptan differs from existing diuretics: it is an aquaretic inhibiting vasopressin V2 receptors in the renal collecting ducts. According to a report that compared the effect of the 32-amino-acid cardiac hormone BNP and tolvaptan, used as monotherapy or in combination, a greater urine output volume was achieved with combination therapy [13]. Therefore, coadministration of tolvaptan and carperitide is considered to have an adequate diuretic effect. Carperitide is a slower-acting diuretic than furosemide and the Prostate Testing for Cancer and Treatment study showed mean hospitalization time to be longer in the carperitide treatment group (54.8 ± 44.9 days) than in the control group (35.9 ± 21.4 days) [4]. Rapid elimination of congestion in ADHF results in a better prognosis [14]. Because congestion should be eliminated in as short a period as possible, coadministration of tolvaptan and carperitide should be used.
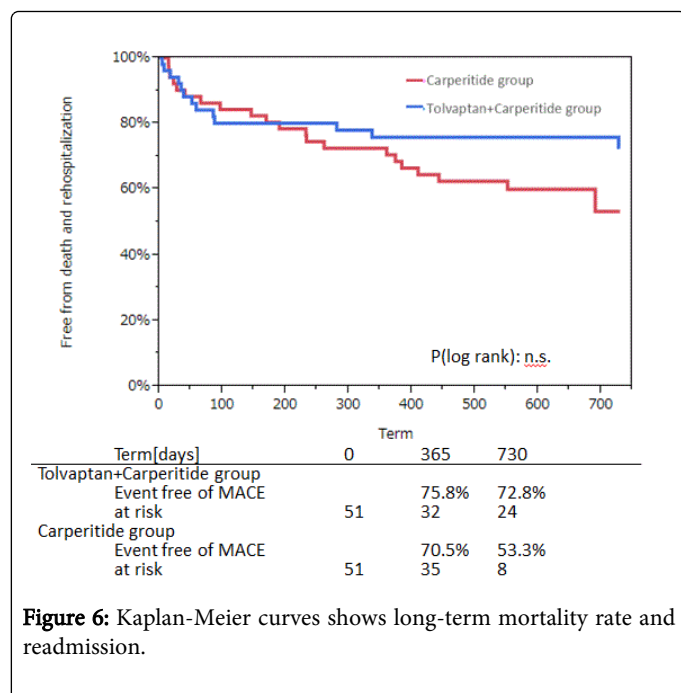
Figure 6: Kaplan-Meier curves shows long-term mortality rate and readmission.

Next, we observed a greater urine output volume in the tolvaptan +carperitide group, whereas the furosemide dose was significantly lower. Diuretics are typically used to treat ADHF. In the Acute Decompensated Heart Failure National Registry, loop diuretics are listed as first-line drugs [15] and the ESC guideline also lists them as the first-line drugs for acute pulmonary edema [16]. In the ATTEND registry, the largest cohort study in Japan involving 4842 patients with acute cardiac failure, loop diuretics were used in 76.2% patients [1]. Loop diuretics act upon the ascending limb of the loop of Henle and have a potent diuretic effect through Na diuresis. However, the ESCAPE study reported a correlation between mortality rate and the dose of loop diuretics administered to treat cardiac failure [17]. The survival rate reportedly decreases when the dose of loop diuretics for treating chronic cardiac failure exceeds 80 mg/day [18]. Loop diuretics promote excretion of the water content from the blood vessels, and their administration activates neurohumoral factors (RAAS) as well as sympathetic activity [19]. Loop diuretics can cause WRF; protecting the kidneys to prevent cardiorenal syndrome in cardiac failure is important [20]. Protecting the kidneys is vital in ADHF; the concept of WRF has been coined, and worsened prognosis and prolonged hospitalization due to WRF have been reported [14,21,22]. In our study, coadministration of tolvaptan and carperitide allowed for a reduction in the dose of furosemide in patients with this type of background and who were receiving treatment for ADHF; an adequate urine output volume was achieved in a short time period. The incidence of WRF was also similar to that in the carperitide treatment group, suggesting that coadministration of tolvaptan and carperitide was also effective for renal protection. Because the RAAS is suppressed upon combined treatment with tolvaptan and BNP [13], coadministration of tolvaptan and carperitide can also reduce activation of the RAAS, which has been a disadvantage of the loop diuretics.

In terms of electrolyte imbalance, there were no symptomatic patients, although one patient receiving tolvaptan and carperitide developed hypernatremia (146 mEq/L). This demonstrated the safety of coadministration of tolvaptan and carperitide and low probability of this combination inducing hypernatremia. In the tolvaptan +carperitide group, patients with low serum Na levels at the start of treatment showed an improvement in hyponatremia. Hyponatremia has been shown to improve overall prognoses. As shown in the ATTEND registry, patients with Na levels of <135 mEq/L had poor prognoses [23].

Carperitide has vasodilating, diuretic, and renal protective effects as well as an inhibitory effect on neurohumoral factors. It has been used in Japan to treat ADHF [4]. According to the ATTEND registry, 58.2% of ADHF patients in Japan were treated with Carperitide [1]. The PROTECT study by Hata et al. has demonstrated the improved prognosis in patients treated with Carperitide for AHDF [4]. In the present study, the 2-year prognosis of patients after treatment for ADHF was the same in the carperitide and tolvaptan+carperitide groups. Therefore, the prognosis for ADHF is similar following treatment with carperitide and loop diuretics.

However, patients with low blood pressure and/or low cardiac output are non-responders to carperitide treatment and thus carperitide can be difficult to use in some ADHF patients [5]. In this study, when we compared patients with ejection fraction<45% and patients with ejection fraction ≥ 45%, there was no difference in urine output volume in 48 h in the carperitide group; however, in the tolvaptan+carperitide group, the urine output volume was significantly higher in patients with ejection fraction<45%. In addition, when we compared patients with low blood pressure, the urine output volume was higher in the tolvaptan+carperitide group. In patients with ejection fraction<30%, the incidence of WRF was significantly lower in the tolvaptan+carperitide group. A significant number of patients in the carperitide group developed hypotension (n=6), but only one did in the tolvaptan+carperitide group. The results of the AVCMA trial, which compared the effects of carperitide and tolvaptan, showed no reduction in blood pressure in the tolvaptan group compared with the carperitide group [12]. Tolvaptan is characterized by excreting only water from the body, resulting in improvement in excess body fluid retention while retaining the intravascular water content. Therefore, this medication has a different mechanism of action from loop diuretics and carperitide, which reduce the intravascular water volume through Na diuresis. Tolvaptan does not affect hemodynamics, making it an effective treatment for patients with reduced cardiac function and hypotension and those who are prone to developing low cardiac output syndrome. Coadministration of tolvaptan and carperitide has been shown to be advantageous for several reasons: (1) it may be possible to reduce the dose of loop diuretics, (2) a high urine output volume can be obtained 48 h after starting treatment, (3) the treatment improves hyponatremia, (4) it is effective also for patients with hypotension or reduced left ventricle function, and (5) it does not worsen the onset of WRF or the patients' prognoses.

There are some limitations to this study. First, this was a single-center study conducted in a small-size study sample. Second, this was not a randomized, double-blinded, placebo-controlled trial. Therefore, there were significant differences between the two groups in terms of patient baselines, including underlying disease and kidney function. In addition, because selection of treatment, tolvaptan+carperitide group or carperitide group was at the discretion of the attending physician, severe patients tended to be included preferentially in the tolvaptan +carperitide group (namely, patients with a history of being treated in hospital for cardiac failure). Third, the study did not evaluate the long-

term outcomes based on the treatments used in the chronic phase. Thus, the possibility that long-term results do not directly reflect the therapeutic effect in the acute phase cannot be ruled out.

Conclusion

In conclusion, in ADHF treatment, coadministration of tolvaptan and carperitide was more effective and safe compared with the carperitide therapy.

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